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6/18/91  
C. Styl  
NE  
Patent  
Case No. HA680a

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Group: 1611  
Examiner: M. Berch  
Applicant: Jeffrey A. Robl  
Serial No.: 08/833,172  
Filed: April 4, 1997  
For: N-FORMYL HYDROXYLAMINE CONTAINING COMPOUNDS  
USEFUL AS ACE INHIBITORS AND/OR NEP INHIBITORS

Princeton, New Jersey 08543-4000  
June 10, 1999

APPEAL BRIEF

To the Assistant Commissioner for Patents:

This is an appeal from the Final Official Action mailed December 15, 1998, and the Advisory Action mailed May 11, 1999, where Claims 1, 6, 7 and 12 to 14 of the above-identified application are finally rejected.

(1) STATUS OF CLAIMS

Claims 1, 6, 7 and 12 to 14 have been finally rejected.

Claims 8 and 15 are objected to as being dependent upon a rejected base Claim 1 and would be allowable if rewritten in independent form.

(2) STATUS OF AMENDMENTS

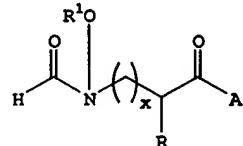
The claims have been amended after final rejection in an "Amendment After Final Rejection" filed ion April 20, 1999. All amendments after final rejection have been entered as per the Advisory Action of May 11, 1999.

Claim 7 has been amended via an accompanying "Second Amendment After Final Rejection" so that it conforms to base Claim 1. The attached "Claims on Appeal" reflect the amendment

to Claim 7. Should this Amendment not be entered, Appellant will submit a new set of Claims on Appeal.

(3) SUMMARY OF INVENTION

Appellant's invention (as claimed in Claim 1) is directed to a compound of the formula



including a pharmaceutically acceptable salt thereof wherein x is 0 or 1,

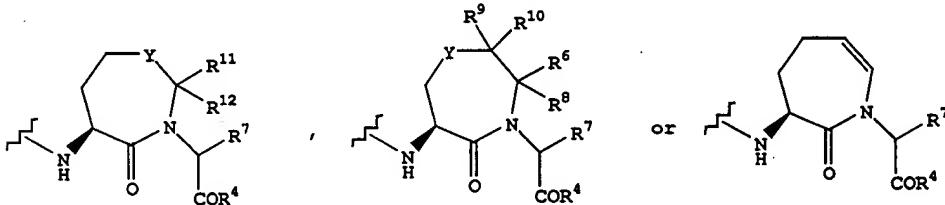
R is H, alkyl, alkenyl, aryl-(CH<sub>2</sub>)<sub>p</sub>-, heteroaryl-(CH<sub>2</sub>)<sub>p</sub>-, cycloheteroalkyl-(CH<sub>2</sub>)<sub>p</sub>-, or

R can be joined together with the carbon to which it is attached to form a 3 to 7 membered ring which may optionally be fused to a benzene ring;

R<sup>1</sup> is H or -COR<sup>2</sup> where R<sup>2</sup> is alkyl, aryl-(CH<sub>2</sub>)<sub>p</sub>-, cycloheteroalkyl-(CH<sub>2</sub>)<sub>p</sub>-, heteroaryl-(CH<sub>2</sub>)<sub>p</sub>-, alkoxy or cycloalkyl-(CH<sub>2</sub>)<sub>p</sub>;

p is 0 or an integer from 1 to 8; and

A is a conformationally restricted dipeptide mimic which has the structure



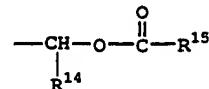
where Y is CH<sub>2</sub>,

$R^7$ ,  $R^8$  and  $R^9$  are independently selected from hydrogen, alkyl, alkenyl, cycloalkyl-( $CH_2$ )<sub>m</sub>-, aryl-( $CH_2$ )<sub>m</sub>- and heteroaryl-( $CH_2$ )<sub>m</sub>-,

where  $m$  is 0 or an integer from 1 to 6;

$R^6$ ,  $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are independently selected from hydrogen, alkyl, alkenyl, cycloalkyl-( $CH_2$ )<sub>p</sub>-, aryl-( $CH_2$ )<sub>p</sub>- and heteroaryl-( $CH_2$ )<sub>p</sub>-; and

$R^4$  is OH, Oalkyl, O-( $CH_2$ )<sub>p</sub>-heteroaryl,



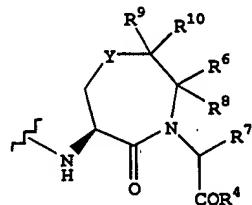
-O-( $CH_2$ )<sub>p</sub>-aryl or  or NR<sub>1</sub>(R<sub>2</sub>), where R<sub>1</sub> and R<sub>2</sub> are independently H, alkyl, aryl, aryl-( $CH_2$ )<sub>p</sub> or heteroaryl;

$R^{14}$  is hydrogen, alkyl, cycloalkyl or phenyl;

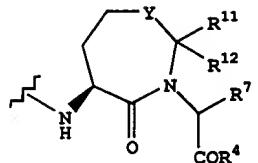
$R^{15}$  is hydrogen, alkyl, alkoxy or phenyl; and

$R^{16}$  is alkyl or aryl-( $CH_2$ )<sub>m</sub>-; wherein the term heteroaryl alone or as part of another group refers to an aromatic ring which may optionally contain at most one sulfur atom or at most one oxygen atom and/or one to four nitrogen atoms, provided that the total number of heteroatoms in the ring is 4 or less, which aromatic ring may be optionally substituted with one, two or three substituents, and which aromatic ring may be fused to a benzene ring or a pyridyl ring to form a bicyclic ring which may be optionally substituted.

In Claim 6, A is defined as



In Claim 7, A is defined as

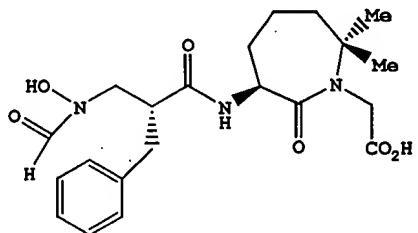


Claims 12 and 13 define a pharmaceutical composition containing a compound as defined in Claim 1.

Claim 14 defines a method of treating hypertension and/or congestive heart failure employing a composition as defined in Claim 12.

Objected to Claim 8 defines the compound of Claim 1 wherein R<sup>1</sup> is H, R is alkyl or arylalkyl, R<sup>4</sup> is OH.

Objected to Claim 15 defines the compound of Claim 1 as



or a pharmaceutically acceptable salt thereof.

(3) ISSUES

Do Claims 1, 6, 7, and 12 to 14 comply with 35 USC § 112, second paragraph.

Subissue A:

Does Claim 1 which includes the term "cycloheteroalkyl" in the definitions of R and R<sup>1</sup> particularly point out and distinctly claim the subject matter with which Appellant regards as his invention?

Subissue B:

Does Claim 1 which includes the definition of "R" as including "R can be joined together with the carbon to which it is attached to form a 3 to 7 membered ring which may be optionally fused to a benzene ring" particularly point out and distinctly claim the subject matter which Appellant regards as his invention?

(4) GROUPING OF CLAIMS

All of the rejected Claims 1, 6, 7 and 12 to 14 stand or fall together.

(5) ARGUMENTS

It is submitted that Claims 1, 6, 7, and 12 to 14 comply with 35 USC § 112, second paragraph in that they particularly point out and distinctly the subject matter which Appellant regards as his invention.

With respect to Subissue A, it is submitted that the term "cycloheteroalkyl" is known to those having ordinary skill in the art and therefore its use in Claim 1 is in compliance with 35 USC § 112.

The law is clear that a patent need not teach what is well known in the art. Spectra-Physics Inc. v. Coherent Inc. (CAFC 1987) 827 F2d 1524, 3 USPQ 2d 1737. However, if Appellant chooses to rely upon general knowledge in the art to render his disclosure enabling, Appellant must show that anyone skilled in the art would have actually possessed the knowledge or information. In re Lange (CCPA 1981) 644 F2d 856, 209 USPQ 288 or one skilled in the art would reasonably be expected to

check the source of such knowledge and information and that such information is readily available and may be located with no more than reasonable diligence. In re Horvath (CCPA 1981) 654 F2d 103, 210 USPQ 689."...public records concerning U.S. patents are likely to be checked, and information therein is reasonably accessible..."Id at 210 USPQ 692.

The Examiner questions the term "cycloheteroalkyl" as being indefinite "since a cycloalkyl cannot have a heteroatom".

Appellant submits that the term "cycloheteroalkyl" is not the same as cycloalkyl. Cycloalkyl is a saturated carbocyclic ring which does not include a heteroatom. However, cycloheteroalkyl is a saturated ring which includes at least one heteroatom. The term "cycloheteroalkyl" is clearly well known to those skilled in the art prior to the filing dates of both the present application and its corresponding provision application.

That the term "cycloheteroalkyl" is known to those having ordinary skill in the art may be seen from the following U.S. Patents all of which issued before the April 4, 1997, filing date of the subject application and the April 12, 1996, filing date of its corresponding provisional application:

<u>U.S. Patent No.</u>	<u>Issue Date</u>
5,290,799	03/01/94
5,332,728 (does not include definition)	07/16/94
5,447,922	09/05/95
5,470,845	11/28/95
5,488,068 (does not include definition)	01/30/96

U.S. Patents which include "cycloheteroalkyl" and issued before the April 4, 1997, filing date of the subject application, but after the April 12, 1996, filing date of its corresponding provisional application are set out below:

<u>U.S. Patent No.</u>	<u>Issue Date</u>
5,543,542	08/06/96
5,550,248	08/27/96
5,561,146	10/01/96
5,567,841	10/22/96

Copies of the relevant portions of the specification and claims of each of the above U.S. patents are enclosed herewith.

In view of the above U.S. patents, it is seen that anyone skilled in the art would have actually possessed knowledge and information with regard to the term "cycloheteroalkyl" as to what is meant by such term. Applying the law set out above to the present situation, it is seen that Appellant need not include the definition of "cycloheteroalkyl" since this term is known to those having ordinary skill in the art. The definition of this term is readily available (prior to the filing date of the subject application) to those skilled in the art (as shown by the listed patents).

Thus, Claim 1, which employs this term, is in compliance with 35 USC § 112, second paragraph with regard to such term. Furthermore, Claims 6, 7, and 12 to 14 which depend from Claim 1 are in compliance with 35 USC § 112, second paragraph as well.

With respect to Subissue B, it is submitted that Claim 1 which includes the language "R can be joined together with the carbon to which it is attached to form a 3 to 7-membered ring which may be optionally fused to a benzene ring" particularly points out and distinctly claims the subject matter which Appellant regards as the invention.

The Examiner maintains that R is a monovalent group. R is a monovalent group where it is "H, alkyl, alkenyl, aryl-(CH<sub>2</sub>)<sub>p</sub>-, heteroaryl-(CH<sub>2</sub>)<sub>p</sub>-, cycloheteroalkyl-(CH<sub>2</sub>)<sub>p</sub>-" as defined in the definition of "R". However, where R is joined together with the carbon to which it is attached to form a 3 to 7-membered ring, R must be a bivalent group. This is inherent in the definition of R. The only way that it is possible for R to be joined to the carbon to which it is attached to form a ring, is that R, in such case, is a bivalent group. The ring formed will have 3 to 7-members and will be a single ring. Where one refers to a "3 to 7-membered ring" it is implicit that the ring is a single ring unless indicated otherwise. The ring thus can be formed with any of the above R groups which will give a 3 to 7-membered ring. Thus, as will be apparent to one skilled in the art, where R is joined together with the carbon to which it is attached to form a 3 to 7-membered ring, in such case, R must be "alkyl" or "alkenyl". Thus, the ring formed would have to be a carbocyclic single or monocyclic ring. If R included heteroaryl or cycloheteroalkyl a 3 to 7-membered ring would not be formed; a bicyclic ring would be formed.

In view of the above, it is submitted that the definition of R is complete and Claim 1 clearly is in compliance with 35 USC § 112, second paragraph. In addition,

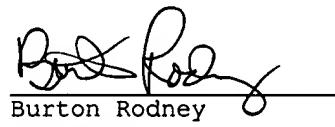
Claims 6, 7, and 12 to 14, which depend from Claims 1 are therefore in compliance with 35 USC § 112, second paragraph.

CONCLUSIONS

It is submitted that in view of the aforementioned arguments, Claims 1, 6, 7, and 12 to 14 clearly comply with 35 USC § 112, second paragraph.

Therefore, it is believed that the Examiner's final rejection of the claims on appeal (Claims 1, 6, 7, and 12 to 14) should be reversed and that such claims should be allowed.

Respectfully submitted,

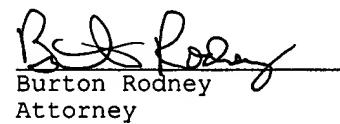


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I hereby certify that this correspondence is being deposited with the United States postal service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on

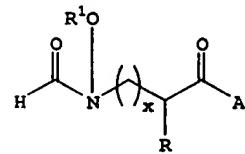


Burton Rodney  
Attorney

Date: June 10, 1999

CLAIMS ON APPEAL

1. A compound of the formula



including a pharmaceutically acceptable salt thereof wherein  
x is 0 or 1,

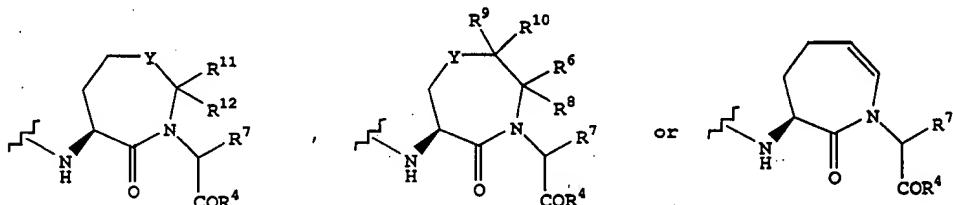
R is H, alkyl, alkenyl, aryl-(CH<sub>2</sub>)<sub>p</sub>-, heteroaryl-(CH<sub>2</sub>)<sub>p</sub>-, cycloheteroalkyl-(CH<sub>2</sub>)<sub>p</sub>-, or

R can be joined together with the carbon to which it is attached to form a 3 to 7 membered ring which may optionally be fused to a benzene ring;

R<sup>1</sup> is H or -COR<sup>2</sup> where R<sup>2</sup> is alkyl, aryl-(CH<sub>2</sub>)<sub>p</sub>-, cycloheteroalkyl-(CH<sub>2</sub>)<sub>p</sub>-, heteroaryl-(CH<sub>2</sub>)<sub>p</sub>-, alkoxy or cycloalkyl-(CH<sub>2</sub>)<sub>p</sub>;

p is 0 or an integer from 1 to 8; and

A is a conformationally restricted dipeptide mimic which has the structure

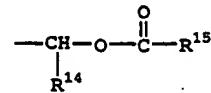


where Y is CH<sub>2</sub>,

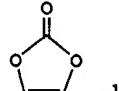
R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> are independently selected from hydrogen, alkyl, alkenyl, cycloalkyl-(CH<sub>2</sub>)<sub>m</sub>-, aryl-(CH<sub>2</sub>)<sub>m</sub>- and heteroaryl-(CH<sub>2</sub>)<sub>m</sub>-,

where m is 0 or an integer from 1 to 6;

$R^6$ ,  $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are independently selected from hydrogen, alkyl, alkenyl, cycloalkyl-( $CH_2$ )<sub>p</sub>-, aryl-( $CH_2$ )<sub>p</sub>- and heteroaryl-( $CH_2$ )<sub>p</sub>-, and



$R^4$  is OH, Oalkyl, O-( $CH_2$ )<sub>p</sub>-heteroaryl,



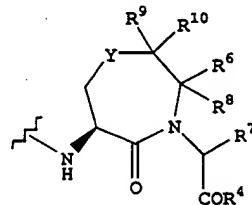
-O-( $CH_2$ )<sub>p</sub>-aryl or  $-\text{CH}_2-$  or  $\text{NR}_1(\text{R}_2)$  where  $R_1$  and  $R_2$  are independently H, alkyl, aryl, aryl-( $CH_2$ )<sub>p</sub> or heteroaryl;

$R^{14}$  is hydrogen, alkyl, cycloalkyl or phenyl;

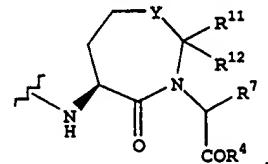
$R^{15}$  is hydrogen, alkyl, alkoxy or phenyl; and

$R^{16}$  is alkyl or aryl-( $CH_2$ )<sub>m</sub>; wherein the term heteroaryl alone or as part of another group refers to an aromatic ring which may optionally contain at most one sulfur atom or at most one oxygen atom and/or one to four nitrogen atoms, provided that the total number of heteroatoms in the ring is 4 or less, which aromatic ring may be optionally substituted with one, two or three substituents, and which aromatic ring may be fused to a benzene ring or a pyridyl ring to form a bicyclic ring which may be optionally substituted.

6. The compound as defined in Claim 1 wherein A is



7. The compound as defined in Claim 1 wherein A is



12. A pharmaceutical composition comprising a compound as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.

13. The pharmaceutical composition as defined in Claim 12 useful in the treatment of hypertension and/or congestive heart failure.

14. A method of treating hypertension and/or congestive heart failure, which comprises administering to a mammalian species a therapeutically effective amount of a composition as defined in Claim 12.

Claims 8 and 15 are allowable.